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EXAMINER
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ART UNIT	PAPER NUMBER
1807	23

DATE MAILED: 09/29/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 7/24/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from 7/23/92. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 104-109, 113-118, 126-137, 141-144, 148, and 149 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-103, 110-112, 119-125, 138-140, and 145-147 have been either cancelled or not entered.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 104-109, 113-118, 126-137, 141-144, 148, and 149 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Supplemental
EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Applicants' arguments and amendments that are herein considered are those in Paper No. 17 (Amendment F), filed 4/21/92, (The amendments to the claims in Paper No. 17 were denied entry, however, the amendments to the specification have been entered.) and those in Paper No. 22 (Amendment G), filed 7/24/92, wherein the amendments to the claims and specification have been entered. These amendments and arguments have been fully considered and they have not been deemed to be persuasive to overcome all of the previously applied rejections. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The Examiner hereby notes that all of the rejections applied herein were also applied in the office action mailed 7/23/92 but were not responded to in the amendment filed 7/24/92 nor overcome by said amendment. Therefore the time to respond to the rejections in the office action mailed 7/23/92 remains unchanged as starting on 7/23/92. In summary this is a supplemental office action mailed to clearly define the rejections still pending against the instant application and does not restart the time to respond that was set in the 7/23/92 office action.

The numbering of claims is not accordance with 37 C.F.R. § 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added,

except when presented in accordance with 37 C.F.R. § 1.121(b), they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 146 and 147 have been renumbered as claims 148 and 149, respectively. The Examiner wishes to point out that Amendment F, filed 4/21/92, presented two claims that were not entered but that caused the two added claims in Amendment G, filed 7/24/92, to be properly numbered as claims 148 and 149 per above 37 C.F.R. § 1.126.

The Examiner wishes to also note that applicants' list of pending claims in Amendment G, filed 7/24/92, is incorrect. The correct list of pending claims is 104-109, 113-118, 126-137, 141-144, 148, and 149.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The most distinctive aspect of the present title is the phrase "modified nucleotides" which is so broad that it lacks any significant indication as to what the invention is directed to. Additionally the title is inclusive of three classes of invention which are: compositions, methods of making, and methods of using. The instantly pending claims are only directed to methods of using and not to compositions or methods of making them.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Applicants have specifically cited certain genes and/or genetic defects in the instant claims as follows:

Claim 131 cites the penicillin resistance gene of Streptococcus pyrogenes.

Claim 131 cites the penicillin resistance gene of Neisseria meningitidis.

Claim 132 cites the tetracycline resistance gene of Staphylococcus aureus.

Claim 132 cites the tetracycline resistance gene of Candida albicans.

Claim 132 cites the tetracycline resistance gene of Pseudomonas aeruginosa.

Claim 132 cites the tetracycline resistance gene of Streptococcus pyrogenes.

Claim 132 cites the tetracycline resistance gene of Neisseria gonorrhoeae.

Claim 133 cites the aminoglycoside resistance gene of Mycobacterium tuberculosis.

Claim 135 cites the "polynucleotide complementary to the nucleic acid which is absent in thalassemic subjects".

Claim 143 cites α-fetal protein and depends from claim 142 which cites the nucleic acid coding for said protein.

Claim 144 cites carcinoembryonic antigen and depends from claim 142 which cites the nucleic acid coding for said protein.

None of the above listed genes or nucleic acids are enabled in the instant disclosure. Since they are specifically cited in the claims as listed above they are critical subject matter for the practice of said listed claims.

Additionally, claim 141, cites detecting abnormal hormonal receptor sites. The specification lacks any enablement or guidance as to what structures, from those given in claim 149, or detection methods are needed to detect "abnormal" receptor sites. Does someone wishing to detect an abnormal site use an abnormal structure from claim 149? Alternatively, can any structure cited in claim 149 be somehow used to detect abnormal receptor sites? In summary, the instant disclosure lacks enablement for the detection method of claim 141 wherein "abnormal" hormonal receptor sites can be detected.

Claims 131-133, 135, 141, 143, and 144 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 104-109, 113-118, 126-137, 141-144, 148, and 149 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to modification of

purines (claim moiety B) only at the 7-position of 7-deazapurines or modification of pyrimidines (claim moiety B) at the 5-position. Said modifications are claimed for attachment of moiety A. This rejection is directed to the non-enablement of the C-8 purine modification. It is noted that applicants cite mercuration as the only method of initiating said modifications of nucleotide bases. On page 3, lines 6-28, of the specification mercuration is discussed wherein Dale et al.(1973) and Dale et al.(1975a) are cited as to C-5 pyrimidine, C-8 purine, and C-7 deazapurine mercuration. No other references or methodology are instantly disclosed to support other base modification methods. Review of the Dale et al. references reveals a lack of support for the C-8 purine modification by mercuration. For example, the abstract of Dale et al.(1973) only cites C-5 pyrimidine and C-7 deazapurine modification. On page 2239, second column, lines 11-14, three sites of modification are suggested (without factual evidence for C-8 purine modification) and then in lines 22-24 the structures of Figure 1 are described as being produced. It is noted that Figure 1 only shows C-5 pyrimidine and C-7 deazapurine modification. The lack of a C-8 purine structure is hereby noted. The only other C-8 purine discussion is on page 2241, second column, in the first sentence of the "DISCUSSION" section. This assertion of C-8 purine modification lacks factual support as to its being prepared as pointed out in the above discussion relating to Figure 1 in the reference by Dale et al.(1973) and therefore lacks enabling support for the instantly claimed C-8

purine modification practice. The other Dale et al.(1975a) reference does not cure this lack of enablement. The abstract of Dale et al.(1975a) does not described C-8 purine modification. On page 2455, first column, lines 31-37, a minor product that may be 8-mercuri-GMP is cited but was not characterized as admitted therein. Such a speculative assignment of structure clearly lacks the disclosure to support the requirement of clear and concise enablement. The accompanying reference by Dale et al.(1975b) discloses only C-5 pyrimidine practice. In summary the scope of the instant enablement does not include C-8 purine modification. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 113-118 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 113 is vague and indefinite in that the polypeptide complexing practice therein claimed is unclear. Since the polypeptide is cited as forming a complex with a compound in accordance with claim 148, it is unclear whether the complex formation is mediated by moiety A or whether the polypeptide can bind anywhere on the compound of claim 148 without specifically binding to moiety A. Which is meant by the complex formation practice of claim 113? Clarification of the claim wording is requested to clarify what complex formation is meant to be claimed with regard to the cited polypeptide.

Claims 108 and 117 are rejected under 35 U.S.C. § 112,

fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claims 108 and 117 are limited to A being a ligand. This is not further limiting from claims 104 and 113, respectively, since the complexing practice of claims 104 and 113 is apparently via binding to moiety A. Such binding can only occur if A is a ligand that can participate is said binding. It is noted that the wording of claim 113 is rejected above as being unclear as to what portion of the compound of claim 148 that the polypeptide complexes with.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 141-144 are rejected under 35 U.S.C. § 101 because there is no evidence given in the instant disclosure that supports the diagnostic utility claimed as detecting malignant cells (claim 141) or diagnosing a tumor cell (claims 142-144). Such diagnostic utility must be supported by evidence that supports definite and currently available utility. See the M.P.E.P. § 608.01(p), section entitled 35 U.S.C. 101.

The disclosure is objected to because of the following informalities:

On page 38, line 10, the word "immunfluorescent" appears to be misspelled.

On page 47, line 20, the word "chromotographic" appears to

be misspelled.

Appropriate correction is required.

Claims 104-109, 113-118, 126-137, 141-144, 148, and 149 are allowable over the prior art of record because the prior art of record does not teach or suggest the instantly claimed methods of use for compositions having the specific points of attachment to the nucleoside residue bases of moiety A.

No claim is allowed.

The Examiner reiterates from the last page of the office action mailed 10/21/91 that none of the references cited in the parent application serial number 06/496,915 or cited on PTO Form 1449 filed 8/7/89 in the instant application have been considered in the instant application because of a continued lack of access to said parent application as well as a lack of copies of the cited references filed in the instant application. Thus the Examiner cannot fulfill the previous request of applicants to consider and make of record those references in the instant application. The Examiner suggests that applicants send copies of any references that applicants wish to have considered in the instant application along with an appropriate PTO Form 1449.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

AM

A. MARSCHEL:am

September 28, 1992

SCOTT A. CHAMBERS
PATENT EXAMINER
GROUP 180